PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 April 2001 (06.04.01)	
International application No. PCT/EP00/06795	**Applicant's or agent's file reference** SANSYL002/MB
International filing date (day/month/year) 27 June 2000 (27.06.00)	**Priority date** (day/month/year) 28 June 1999 (28.06.99)
Applicant ANDRE, Frédéric et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

24 January 2001 (24.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

REC'D 02 OCT 2001

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SANSYL002/MW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06795	27/06/2000	28/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/50		
Applicant SANOFI-SYNTHELABO et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	28.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Couzy, F Telephone No. +49 89 2399 7503

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16 as originally filed

Claims, No.:

1-22 with telefax of 14/09/2001

Drawings, No.:

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6, 9-12, 15-22
	No:	Claims	1-3, 7-8, 13-14
Inventive step (IS)	Yes:	Claims	4-6, 15-22
	No:	Claims	1-3, 7-12, 13-14
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R Item V

Reasoned statement under Article 35 (2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 97 23219 A (LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM) 3 July 1997 (1997-07-03)

D2: WO 95 03052 A (WARNER-LAMBERT) 2 February 1995 (1995-02-02)

D3: EP-A-0 386 967 (YAMANOUCHI) 12 September 1990 (1990-09-12)

D4: WO 93 09785 A (PROCTER & GAMBLE) 27 May 1993 (1993-05-27)

D5: EP-A-0 908 177 (GOLD, OSCAR) 14 April 1999 (1999-04-14)

D6: WO 99 48498 A (GEA FARMACEUTISK FABRIK) 30 September 1999 (1999-09-30)

V.2 Novelty (Art. 33 (2) PCT) and inventive step (Art. 33 (3) PCT)

The subject-matter of claims 1-3, 7-8, and 13-14 is not new in light of Article 33(2) PCT. Additionally, the subject-matter of dependent claim 9-12 does not contain an inventive step in the sense of Article 33(3) PCT.

V.2.a Indeed, the coated core and the pharmaceutical dosage form of independent claims 1 and 13, as well as their embodiments of claims 2-3, 7-9, and 14, are disclosed in:

Claim 1: D1 (p.2 li.5-8, p.5 li.31-36): the core of D1 consists of a coated inert support

Claim 2: D1 (p.4 li.23-24 and claim 6)

Claim 3: D1 (p.5 li.31-36), D3 (col.3 li.9, col.3 li.28-29)

Claim 7: D1 (p.2 li.5-8), D3 (col.2 li.1)

Claim 8: D1 (example 5: p.15 li.2, p.21 li.22-23 and 27)

Claim 13: D1 (p.2 li.5-6, p.5 li.31-36, claim 20),

Claim 14: D1 (p.2 li.5-6, p.5 li.31-36),

The functional features "producing a timed pulse release" and "that diffuses into the polymer coating and at a given level provokes a sudden change in the coating's properties" do not allow to unambiguously differentiate the claimed subject-matter from the prior art, because if the technical features are the same the possibility exists that these functional features may also be present.

V.2.b That the granules may be formed as a tablet is not new (claim 10). Therefore, that these granules may be compressed under the form of minitablets is obvious for a man skilled in the art, unless a specific technical problem were identified and solved. Such is not the case in the current application, thus **subject-matter of dependent claim 10 does not contain an inventive step.**

V.3.c Document D2 (p.5-9) discloses a controlled drug delivery system comprising a core made of immediate release pellets, which may include a surfactant (p.10 li.36), and a "sustaining layer" which may include a polymethacrylate copolymer of the Eudragit® type. However, the ammonio methacrylate copolymers are not specifically disclosed. The system of D2 is suitable for a time pulse delivery (curves CR1, CR2, and CR9 on Figures 2B, 3A, 4B, and 6). The core may be separated from the coating by a layer of water-soluble polymer (p.8 li.2-7). The Demand does not disclose a specific advantage of selecting an ammonio methacrylate copolymer vs. the copolymers of D2. Thus, **the subject-matter of claims 1, 8-12, 13-14 also lacks an inventive step in light of D2 alone.**

V.3 **The subject-matter of all claims is industrially applicable in the sense of Article 33 (4) PCT.**

Re Item VII

Certain defects in the international application

VII.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3 is not mentioned in the description, nor are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

VIII.1 **Independent claim 1 (and claims dependent thereof) does not meet the requirements of Article 6 PCT** in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to

be achieved ("producing a timed pulse release", being a means that diffuses ... properties"), which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

VIII.1 The **unclear and unnecessary wordings** "not limiting the scope of the present invention" p.6 li.13, and "without limiting it" on p.11 li.24, result in **lack of clarity** as regards the subject-matter of the claims when interpreted in light of the description (Art.6 PCT).

VIII.2 There is a **discrepancy** between claim 22 and the description on p.10 li.30-31, because the description mentions that the tablet is **press** coated, and not simply coated as stated in claim 22. This confers **lack of clarity of claim 22** when interpreted in light of the description (Art. 6 PCT).

VIII.3 The technical term "non-pareil" on page 11 li.29 appears to be a trade mark and **has no generally accepted meaning**, in contrary to the requirements of Rule 10 (e) PCT.

VIII.4 The term "type A or B" in claim 3 **has no generally accepted meaning**, in contrary to the requirements of Rule 10 (e) PCT. Thus, **subject-matter of said claim 3 is unclear (Art.6 PCT).**

INTERNATIONAL SEARCH REPORT

Inter. ional Application No
PCT/EP 00/06795

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 97 23219 A (LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM) 3 July 1997 (1997-07-03) claims 1,6,14,15 page 5, line 31 - line 36	1-3, 7-10,13, 14 11,12
Y	WO 95 03052 A (WARNER-LAMBERT) 2 February 1995 (1995-02-02) claim 1 page 7, line 26 -page 8, line 7 page 8, line 27 -page 9, line 22	11,12
X	EP 0 386 967 A (YAMANOUCHI) 12 September 1990 (1990-09-12) claims 1-3 column 3, line 5 - line 29 column 4, line 11 - line 13	1,3, 7-10,13, 14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 09785 A (PROCTER & GAMBLE) 27 May 1993 (1993-05-27) the whole document	1-22
A	EP 0 908 177 A (GOLD, OSCAR) 14 April 1999 (1999-04-14) the whole document	1-22
P,A	WO 99 48498 A (GEA FARMACEUTISK FABRIK) 30 September 1999 (1999-09-30) the whole document	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten ...nal Application No
PCT/EP 00/06795

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/EP 00/06795

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		US 5935602 A	10-08-1999
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WO 9948498 A	30-09-1999	DK 39798 A	21-09-1999
		AU 2714899 A	18-10-1999

Client Identifier: SS/SANSYL002/PED
Date of Request: 12/05/01
The Current Database is WPI
Your Terms and Connectors Query:

PN(WO 9723219)

199732

Sustained release microgranules comprise carrier coated with active layer of diltiazem, surfactant and binder, then covered with release layer - useful in treatment of arterial hypertension, providing solubilisation and absorption of active agent despite absence of water-soluble acid

Patent Assignee: LAB PROD ETHIQUES ETHYPHARM (ETHI-N)
Inventor: DEBREGEAS P; LEDUC G; OURY P; SUPLIE P
Number of Countries: 074
Number of Patents: 015
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9723219	A1	19970703	WO 96FR2040	A	19961223	199732	B
FR 2742660	A1	19970627	FR 9515361	A	19951222	199733	
ZA 9610776	A	19970923	ZA 9610776	A	19961220	199744	
AU 9711983	A	19970717	AU 9711983	A	19961223	199745	
NO 9802738	A	19980821	WO 96FR2040	A	19961223	199843	
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EP 868184	A1	19981007	EP 96943156	A	19961223	199844	
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CN 1207681	A	19990210	CN 96199764	A	19961223	199925	
BR 9612225	A	19990713	BR 9612225	A	19961223	199939	
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NZ 324739	A	20000128	NZ 324739	A	19961223	200015	
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US 9891646	A	19981125					

Priority Applications (No Type Date): FR 9515361 A 19951222
Cited Patents: EP 149920; EP 263083; EP 318398; EP 322277; WO 9309767
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9723219	A1	F	70	A61K-031/55	

Designated States (National): AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

FR 2742660	A1		15	A61K-031/55	

ZA 9610776 A 70 A61K-000/00
AU 9711983 A B42D-015/10 Based on patent WO 9723219
NO 9802738 A A61K-000/00
EP 868184 A1 F A61K-031/55 Based on patent WO 9723219
Designated States (Regional): AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT RO SE SI
CN 1207681 A A61K-031/55
BR 9612225 A A61K-031/55 Based on patent WO 9723219
NZ 324739 A A61K-031/55 Based on patent WO 9723219
HU 9904129 A2 A61K-031/55 Based on patent WO 9723219
JP 2000506500 W 70 A61K-031/554 Based on patent WO 9723219
AU 721949 B A61K-031/55 Previous Publ. patent AU 9711983
Based on patent WO 9723219
KR 99076717 A A61K-031/55 Based on patent WO 9723219
MX 9805121 A1 A61K-031/55
US 6228395 B1 A61K-009/58 Based on patent WO 9723219

Abstract (Basic): WO 9723219 A

Sustained release microgranules comprise a layer to ensure sustained release of an active agent and a neutral, granular carrier coated with an active layer containing diltiazem or one of its salts, a surfactant and binder.

The layer provides slow or rapid release of the active agent. The layer providing slow sustained released is itself coated with a second layer containing the active agent, surfactant and binder and over this an external layer for rapid release of (I) contained in the second active layer. An intermediate layer is optionally intercalated between the slow release layer and its coating.

USE - Diltiazem is a calcium antagonist which is used in the treatment of arterial hypertension.

ADVANTAGE - The microcapsules are easy to make and despite the absence of a water-soluble organic acid, active agent solubilisation and absorption levels are equivalent to those achieved in the presence of an acid.

Dwg.0/1

Title Terms: SUSTAINED; RELEASE; COMPRISE; CARRY; COATING; ACTIVE; LAYER; DILTIAZEM; SURFACTANT; BIND; COVER; RELEASE; LAYER; USEFUL; TREAT; ARTERY; HYPERTENSIVE; SOLUBLE; ABSORB; ACTIVE; AGENT; ABSENCE; WATER; SOLUBLE; ACID

Derwent Class: A96; B02; B07; P73; P76

International Patent Class (Main): A61K-000/00; A61K-009/58; A61K-031/55; A61K-031/554; B42D-015/10

International Patent Class (Additional): A61K-009/16; A61K-009/50; A61K-009/52; A61K-047/20; A61K-047/24; A61P-009/12; B32B-007/06; B32B-007/12; C07D-281/10; C09J-007/02

File Segment: CPI; EngPI

Manual Codes (CPI/A-N): A12-V01; B06-F03; B12-M10A; B14-F02B

Chemical Fragment Codes (M1):

04 F011 F012 F423 H2 H211 H7 H713 H721 J5 J521 L9 L941 M210 M212 M273 M281 M320 M413 M423 M431 M510 M521 M530 M540 M782 M903 M904 R032 R052 V743 R00546-M R00546-Q 01825

Chemical Fragment Codes (M2):

01 A111 A960 C710 K0 K4 K421 M225 M231 M272 M281 M320 M411 M431 M620 M630 M782 M903 M904 Q616 R032 R052 R05327-M

02 D015 E660 G013 G100 H1 H103 H181 H2 H211 H5 H541 H8 J0 J011 J2 J221 J5 J521 L9 L941 M1 M113 M210 M211 M262 M272 M273 M281 M282 M312 M321 M332 M342 M383 M391 M412 M431 M511 M520 M531 M540 M782 M903 M904 P526 R032 R052 R04284-M 01825

03 G011 G100 J0 J012 J2 J232 M210 M212 M272 M282 M320 M414 M431 M510 M520 M531 M540 M782 M903 M904 M910 Q614 R032 R052 R00507-M 01825

Polymer Indexing (PS):

<01>

001 018; G0635 G0022 D01 D12 D10 D23 D22 D31 D41 D51 D53 D58 D75 D86 F71; H0000; S9999 S1412 S1401

002 018; ND01; Q9999 Q7250; Q9999 Q8037 Q7987; Q9999 Q7523; N9999 N7330 N7023; K9723
003 018; Q9999 Q6791
<02>
001 018; G0384-R G0339 G0260 G0022 D01 D12 D10 D26 D51 D53 D58 D63 F41 F89; H0000; H0011-R; S9999 S1423 S1401; P0088
002 018; ND01; Q9999 Q7250; Q9999 Q8037 Q7987; Q9999 Q7523; N9999 N7330 N7023; K9723
003 018; N9999 N7147 N7034 N7023; Q9999 Q7114-R
<03>
001 018; R00351 G1558 D01 D23 D22 D31 D42 D50 D73 D82 F47; H0000; P0055 ; P8004 P0975 P0964 D01 D10 D11 D50 D82 F34; M9999 M2153-R; M9999 M2186
002 018; ND01; Q9999 Q7250; Q9999 Q8037 Q7987; Q9999 Q7523; N9999 N7330 N7023; K9723
Ring Index Numbers:
01825
Derwent Registry Numbers: 0507-U; 0546-S; 0546-U
Specific Compound Numbers: R05327-M; R04284-M; R00507-M; R00546-M; R00546-Q

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/EP 00/06795

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 97 23219 A (LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM) 3 July 1997 (1997-07-03) claims 1,6,14,15 page 5, line 31 - line 36	1-3, 7-10,13, 14 11,12
Y	WO 95 03052 A (WARNER-LAMBERT) 2 February 1995 (1995-02-02) claim 1 page 7, line 26 -page 8, line 7 page 8, line 27 -page 9, line 22	11,12
X	EP 0 386 967 A (YAMANOUCHI) 12 September 1990 (1990-09-12) claims 1-3 column 3, line 5 - line 29 column 4, line 11 - line 13	1,3, 7-10,13, 14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/EP 00/06795

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 09785 A (PROCTER & GAMBLE) 27 May 1993 (1993-05-27) the whole document ---	1-22
A	EP 0 908 177 A (GOLD, OSCAR) 14 April 1999 (1999-04-14) the whole document ---	1-22
P,A	WO 99 48498 A (GEA FARMACEUTISK FABRIK) 30 September 1999 (1999-09-30) the whole document -----	1-22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten nal Application No
PCT/EP 00/06795

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter...nal Application No
PCT/EP 00/06795

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9309785 A		US 5622721 A	22-04-1997
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14

REC'D 02 OCT 2001
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SANSYL002/MW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/06795	27/06/2000	28/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/50		
Applicant SANOFI-SYNTHELABO et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	28.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Couzy, F Telephone No. +49 89 2399 7503

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/06795

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16 as originally filed

Claims, No.:

1-22 with telefax of 14/09/2001

Drawings, No.:

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6, 9-12, 15-22
	No:	Claims	1-3, 7-8, 13-14
Inventive step (IS)	Yes:	Claims	4-6, 15-22
	No:	Claims	1-3, 7-12, 13-14
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35 (2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 97 23219 A (LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM) 3 July 1997 (1997-07-03)

D2: WO 95 03052 A (WARNER-LAMBERT) 2 February 1995 (1995-02-02)

D3: EP-A-0 386 967 (YAMANOUCHI) 12 September 1990 (1990-09-12)

D4: WO 93 09785 A (PROCTER & GAMBLE) 27 May 1993 (1993-05-27)

D5: EP-A-0 908 177 (GOLD, OSCAR) 14 April 1999 (1999-04-14)

D6: WO 99 48498 A (GEA FARMACEUTISK FABRIK) 30 September 1999 (1999-09-30)

V.2 Novelty (Art. 33 (2) PCT) and inventive step (Art. 33 (3) PCT)

The subject-matter of claims 1-3, 7-8, and 13-14 is not new in light of Article 33(2) PCT. Additionally, the subject-matter of dependent claim 9-12 does not contain an inventive step in the sense of Article 33(3) PCT.

V.2.a Indeed, the coated core and the pharmaceutical dosage form of independent claims 1 and 13, as well as their embodiments of claims 2-3, 7-9, and 14, are disclosed in:

Claim 1: D1 (p.2 li.5-8, p.5 li.31-36): the core of D1 consists of a coated inert support

Claim 2: D1 (p.4 li.23-24 and claim 6)

Claim 3: D1 (p.5 li.31-36), D3 (col.3 li.9, col.3 li.28-29)

Claim 7: D1 (p.2 li.5-8), D3 (col.2 li.1)

Claim 8: D1 (example 5: p.15 li.2, p.21 li.22-23 and 27)

Claim 13: D1 (p.2 li.5-6, p.5 li.31-36, claim 20),

Claim 14: D1 (p.2 li.5-6, p.5 li.31-36),

The functional features "producing a timed pulse release" and "that diffuses into the polymer coating and at a given level provokes a sudden change in the coating's properties" do not allow to unambiguously differentiate the claimed subject-matter from the prior art, because if the technical features are the same the possibility exists that these functional features may also be present.

V.2.b That the granules may be formed as a tablet is not new (claim 10). Therefore, that these granules may be compressed under the form of minitablets is obvious for a man skilled in the art, unless a specific technical problem were identified and solved. Such is not the case in the current application, thus **subject-matter of dependent claim 10 does not contain an inventive step.**

V.3.c Document D2 (p.5-9) discloses a controlled drug delivery system comprising a core made of immediate release pellets, which may include a surfactant (p.10 li.36), and a "sustaining layer" which may include a polymethacrylate copolymer of the Eudragit® type. However, the ammonio methacrylate copolymers are not specifically disclosed. The system of D2 is suitable for a time pulse delivery (curves CR1, CR2, and CR9 on Figures 2B, 3A, 4B, and 6). The core may be separated from the coating by a layer of water-soluble polymer (p.8 li.2-7). The Demand does not disclose a specific advantage of selecting an ammonio methacrylate copolymer vs. the copolymers of D2. Thus, **the subject-matter of claims 1, 8-12, 13-14 also lacks an inventive step in light of D2 alone.**

V.3 **The subject-matter of all claims is industrially applicable in the sense of Article 33 (4) PCT.**

Re Item VII

Certain defects in the international application

VII.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3 is not mentioned in the description, nor are this/these document/s identified therein.

Re Item VIII

Certain observations on the international application

VIII.1 **Ind p nd nt claim 1 (and claims dependent thereof) does not m et the requir ments of Articl 6 PCT** in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to

be achieved ("producing a timed pulse release", being a means that diffuses ... properties"), which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

VIII.1 The **unclear and unnecessary wordings** "not limiting the scope of the present invention" p.6 li.13, and "without limiting it" on p.11 li.24, result in **lack of clarity** as regards the subject-matter of the claims when interpreted in light of the description (Art.6 PCT).

VIII.2 There is a **discrepancy** between claim 22 and the description on p.10 li.30-31, because the description mentions that the tablet is **press** coated, and not simply coated as stated in claim 22. This confers **lack of clarity of claim 22** when interpreted in light of the description (Art. 6 PCT).

VIII.3 The technical term "non-pareil" on page 11 li.29 appears to be a trade mark and **has no generally accepted meaning**, in contrary to the requirements of Rule 10 (e) PCT.

VIII.4 The term "type A or B" in claim 3 **has no generally accepted meaning**, in contrary to the requirements of Rule 10 (e) PCT. Thus, **subject-matter of said claim 3 is unclear (Art.6 PCT).**

PHARMACEUTICAL DOSAGE FORMS FOR CONTROLLED RELEASE PRODUCING AT LEAST A TIMED PULSE

The present invention relates to controlled release dosage forms producing at least a timed pulse, that is a rapid and complete controlled release of a pharmaceutical substance a fixed time after administration.

Most pharmaceutically active substances administrated orally are given as conventional immediate release or rapid release forms. Thus, provided drug release and absorption are rapid, the concentration time profile of the active substance in the blood or other body compartment depends on the kinetics of elimination of the molecule from the body, and on the distribution and kinetics of distribution in different body compartments and tissues.

This limits the time the drug spends in the body components and thus the time of action of the drug. For this reason, in order to increase the residence time of the drug, prolonged release dosage forms are used, allowing less frequent dosing. In the past, it has often been considered for most drugs that there is an optimum plasma level, and thus the best formulation will be one that gives blood plasma concentration profiles as near constant as possible, and allows reduced dosing frequency.

However such release patterns giving constant plasma levels are not always optimal.

Physiological processes are indeed most of the time not constant over time and circadian rhythms have been shown for almost all bodily functions, as well as symptoms of certain diseases.

For example, myocardial infarction and ischemia and angina pectoris, attacks are more frequent in morning hours 6 - 12 am, and occur particularly in the 4 hours following awaking. Thus it would be preferable in the treatment of these diseases to ensure relatively high blood levels of the drug over that period. For example, an evening administration at 21.00 could then imply an increased release rate about 7-10 hours after administration.

Examples of other diseases and symptoms showing a circadian pattern are inflammatory diseases, nocturnal asthma, migraine headache, ulcer, including perforated ulcer, intractable pain and pain from rheumatoid arthritis.

Controlled release dosage forms producing a timed pulse are therefore particularly adapted in the treatment of the here above cited diseases and symptoms thereof. In other words, they can be used for the corresponding chronotherapeutic treatments.

It is also well known that drug release in the form of a pulse rather than a steady slow release may reduce loss by a saturable first-pass effect as in the case of levadopa or propoxyphene. In addition, certain receptors are inactivated by prolonged stimuli, and a pulsed, or on-off delivery can overcome this effect.

As another advantage timed release can allow targeting of a drug to a given site of the gastrointestinal tract, in particular the colon. This depends on the near constant transit time of a pharmaceutical dosage form through the small intestine. A rapid release of the drug in the colon may have advantages in allowing a high local concentration and improved absorption, since absorption of many drugs is much slower and less complete from the colon than from the small intestine, and absorption may become the rate-limiting step rather than release from the dosage form.

It is therefore clear that formulations producing a timed pulse are useful, for example, as described above, for obtaining a non-constant blood plasma concentration profile compatible with and optimal for the therapeutic objective, or for compensating the differences in the rate and extent of absorption in different portions of the gastro-intestinal tract, and so obtaining minimally fluctuating blood levels over the entire dosing period.

Dosage forms for controlled release producing at least a timed pulse may also be useful as complementary treatment of an initial treatment. For example, the effect of an initial active substance, which acts rapidly may be suppressed or completed by a second active substance released a fixed time after administration of the dosage form comprising both of the active substances.

Until now, one of the known methods of achieving a timed pulse from a single galenic entity consists in coating a core comprising the active substance with a polymer coating comprising at least one or more methacrylate copolymers containing quaternary ammonium groups. These are referred to as ammonio methacrylate copolymers.

Dosage forms formulated from these here above described coated cores can give sigmoidal release profiles but not real timed pulse profiles. In other words the achieved release rate is often not rapid enough. And another disadvantage of this technique is related to the fact that a large amount of the drug is not released from the coated cores.

The first object of the present invention is then related to a pharmaceutical dosage form for a timed pulse release, whereby the release rate is zero or very low during a fixed time and then the whole of the drug comprised in the dosage form is released rapidly.

Indeed the applicant has found surprisingly that the addition of small quantities of a surfactant into a core comprising the active substance, which is coated with at least one or more ammonio methacrylate copolymer, as described above, give a delayed accelerated pulse, and substantially more complete release of the drug.

The term "particle" in the whole description encompasses all galenic entities variously known as pellets, beads, granules or spheroids.

The core may be a tablet or a particle and the dosage form may be monolithic, that is a single tablet, or multiparticulate, that is either several tablets or a large number of particles. Multiple particles may be within a capsule. Alternatively a large number of particles may be compressed into a tablet which disintegrates in aqueous fluids, releasing the particles.

For reasons of simplicity, in the whole description, the resulting particle or tablet is named "delayed release particle", or "delayed release tablet" or more generally "delayed release coated core".

Thus the present invention, as a first object, provides delayed release coated cores comprising an active substance in their core and a polymer coating comprising at least one or more ammonio methacrylate copolymer, characterised in that the core comprises at least a surfactant.

The present invention also provides monolithic or multiparticulate pharmaceutical dosage forms comprising such delayed release coated cores, producing one unique timed pulse.

The present invention also provides the method of manufacture of the delayed release coated cores and the pharmaceutical dosage forms containing them.

Ammonio methacrylate can be of two types, A and B. These are for example marketed by Röhm Pharma as Eudragit® RS and Eudragit® RL, respectively. Type A, like Eudragit® RS, is relatively impermeable to water and small molecules, and Eudragit® RL is relatively permeable.

According to the invention other polymers and pharmaceutical adjuvants well known to persons with ordinary skill in the art of pharmaceutical formulation may also be incorporated in the coating. The polymers may include cellulosic derivatives such as ethylcellulose or hydroxypropylmethylcellulose (ou hypromellose), and other adjuvants are plastifiers such as diacetylated monoglycerides or triethyl citrate, and antitack agents such as talc.

According to the present invention the additional surfactant is either cationic or amphoteric and/or zwitterionic in nature.

In fact, an additional surfactant diffuses into the polymer coating, and at a given level provokes a sudden change in the film's properties.

Examples of such cationic surfactants are trimethyl-dimyristoyl-ammonium propionate, dimethyl-dioctadecyl-ammonium bromide, trimethyl-cetyl-ammonium bromide (CTAB), dimethyl-didodecyl-ammonium bromide (DDAB(12)), benzalkonium chloride, cetylpyridinium chloride or cetrimide.

Other salts of the above cationic surfactants may equally be employed.

Preferred examples of cationic surfactants are benzalkonium chloride and cetylpyridinium chloride.

Examples of zwitterionic surfactants are the N-alkylbetaines, the C-alkylbetaines, the N-alkylamidobetaines such as cocamidopropylbetain ; the N-alkylglycines and the phosphatidylcholines or lecithins.

The present invention also extends to the use of mixtures of cationic and/or zwitterionic surfactants especially mixtures of the afore mentioned surfactants.

Suitable active substances may be selected from, for example, hormones, polysaccharides, polypeptides, steroids, hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatories, muscle contractants, sympathomimetics, polypeptides and proteins capable of eliciting physiological effects, diuretics, lipid regulating agents, antiandrogenic agents, neoplastics, antineoplastics, hypoglycemics, antienteritis agents, and diagnostic agents.

Exemples of active substance useful in this invention include diltiazem, theophylline, felodipine, verapamil, clonidine, acebutolol, alprenolol, betaxolol, metoprolol, nadolol, propranolol, timolol, captopril, enalapril, fosinopril, tiapamil, gallopamil, amlodipine, nitrendipine, nisoldipine, nicardipine, felodipine, molsidamine, indomethacin, sulindac, indoprofen, ketoprofen, flurbiprofen, fenbufen, fluprofen, diclofenac, tiaprofenic acid, naproxen, mizolastin, terbutaline, salbutamol, betamethasone, prednisone, methylprednisone, dexamethasone, prednisolone, sumatriptan, naratriptan, cimetidine, ranitidine, famotidine, nizatidine , omeprozole, morphine, fenoprofen, ibuprofen, ketoprofen, alclofenac, mefenamic, alfuzosin, prazosin, tamsulosin, levodopa and methyldopa, their salts and pharmacologically active esters.

In advantageous embodiments, dosage forms may be formulated in order to obtain a timed pulse release independent of the pH. The preferred manner to achieve such a release, in the case of a basic drug is to add a pharmaceutically acceptable organic acid into the dosage form, according to methods known from one skilled in the art. Such dosage forms are preferred.

These pharmaceutically acceptable organic acids can be chosen for example among maleic, tartaric, malic, fumaric, lactic, citric, adipic or succinic acid and their acid salts where these exist, in the form of racemates or isomers, where these exist. According to the invention, acids particularly preferred are tartaric, fumaric, citric, and succinic and their acid salts.

The amount of cationic or zwitterionic surfactant which may be used with the present invention may vary but preferably is between 10 and 50% with respect to the amount of ammonio methacrylate copolymer in the coating.

The dosage forms according to the present invention include capsules, tablets, multicoated tablets, granulates.

Various formulations, not limiting the scope of the present invention, illustrating the first object of the invention, that is pharmaceutical dosage forms producing one unique timed pulse, are described hereafter:

(1) Delayed release particles containing a drug :

These are particles of dimension for example 0.2 to 2 mm diameter, comprising in addition to the drug at least a cationic surfactant in the core and with a polymer coating comprising at least one or more ammonio methacrylate copolymers.

The particles may be manufactured by any of the methods well known to one skilled in the art: granulation in a high speed granulator, extrusion followed by spheronisation, gradual coating of a sphere with a mixture comprising the drug etc. The sphere may consist of any commonly used pharmaceutical substance, sucrose, sucrose and starch, mannitol, microcrystalline cellulose.

The particles are coated for delayed release with a coating comprising one or more ammonio methacrylate copolymers. In addition the coating may comprise one or more other polymers impermeable to water and to drug molecules, such as ethylcellulose, cellulose acetate, cellulose acetate butyrate, polyvinyl chloride, polyvinylacetate. The coating may also comprise one or more polymers which are permeable to water, such as hydroxypropylmethylcellulose, hydroxyethylcellulose.

The composition of the mixture and the amount of coating applied is adjusted to allow gradual hydration of the film and a delayed release profile.

The core may comprise other substances necessary, in particular an organic acid to maintain the pH at the interior of the particle constant. In an advantageous embodiment of the invention the core is separated from the outer coating by a layer of water soluble polymers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, and polyvinylpyrrolidone.

The particles may be filled in a unique dosage form as a gelatin capsule.

(2) Delayed release tablets comprising a drug and at least a cationic surfactant in the core and with a polymer coating comprising at least one or more ammonio methacrylate copolymers.

These are formulated by the methods well known to one skilled in the art.

In addition to the drug and the cationic surfactant they can comprise inert pharmaceutical excipients, including one or more diluants, for example microcrystalline cellulose, lactose, mannitol, starch ; and may contain other excipients.

These can include one or more binders, for example hydroxypropylmethylcellulose, ethylcellulose and povidone, lubricants, for example magnesium stearate, glyceryl stearate, and glyceryl behenate, disintegrants, for example crospovidone, sodium starch glycolate and croscarmellose, glidants, for example talc and colloidal silicon dioxide. In particular a pharmaceutically acceptable acid may be added to ensure liberation of the basic active substances independent of the pH of the external medium.

The tablets can be prepared by compression of a simple mixture or a granulate, followed by coating with a polymer solution.

Minitablets which are also emcompassed in the invention are tablets of dimension 3 mm or less. They can be used for achieving dosage forms for timed pulse release. They can be manufactured using the same components as described above.

The delayed release tablets can be coated with a layer of polymer coating similar to those described for the multiparticulate systems above. However except in the case of the minitablets some modification of the coating may be required because of the difference in surface area of the dosage form.

It is usually necessary to apply a thicker coating on the tablet than on the particles, and thus a higher proportion of water-permeable polymers can be required in the coating composition. The core may also be separated from the outer coating by a layer of water soluble polymers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, and polyvinylpyrrolidone.

The delayed release tablets or minitablets may be used alone. The minitablets may also been filled into envelopes such as hard gelatine capsules.

Moreover, as a further object, the invention also encompasses all dosage forms comprising delayed release coated cores according to the invention combined together to give a "stepped" release profile or with other galenic entities. These other galenic entities can for example be immediate or sustained release systems.

As described above, these further dosage forms can also be used for example in chronotherapeutic treatments, to overcome the first pass effect, or to improve the absorption according to a given part of the gastrointestinal tract.

The other galenic entities may contain the same active substance as the delayed release entity or a different active substance. Indeed, when comprising two different active substance, dosage forms can for example be formulated in order to obtain the complementary treatment described hereinabove.

In particular an object of the present invention is related to pharmaceutical compositions for timed dual release, whereby a first release pulse occurs immediately and a second release pulse is delayed to a fixed time.

Examples of the different types of profiles which may be obtained by combining formulations according to the invention with other galenic entities are shown in figure 1.

The following formulations illustrate this further object of the invention, that is dosage forms comprising delayed release coated cores according to the invention combined together to give a "stepped" release profile or with other galenic entities :

(1) Capsule comprising the delayed release particles or minitablets according to the invention and an immediate and/or sustained release entities

The required amount of delayed release particles or minitablets according to the invention are combined with one or both of the following

(i) immediate release (uncoated) particles or minitablets or an immediate release granulate or powder

(ii) sustained release particles or minitablets (coated, slow release)

in hard gelatine capsules of the required size.

Particles or minitablets with different delayed release profiles may also be combined to give a "stepped" release profile.

(2) A tablet comprising delayed release particles according to the invention imbedded in a rapidly disintegrating matrix.

The matrix may also comprise the drug substance. Sustained (slow) release particles may be included in addition to the delayed release particles.

Alternatively the tablet may consist of a mixture of delayed release particles and of immediate release non-coated particles comprising the active substance, imbedded in a matrix free from the drug.

Alternatively the delayed release particles may be furthermore coated with a layer comprising the drug and other excipients allowing immediate release from that layer, imbedded in a matrix free from the drug.

Alternatively the delayed release tablet may consist of one or more layers comprising delayed release particles comprising the drug, imbedded in a matrix free from the drug and one or more layers comprising the drug in an immediate release matrix.

The matrix surrounding the particles should preferably be formulated so that the compression into tablets does not interfere with the integrity of the membrane surrounding the pellets. On contact with fluid the tablet disintegrates, releasing the drug rapidly, from the matrix, or the immediate release pellets, or from the immediate release particle coating, or from the immediate release layer, and then, after a fixed interval of time, releases the drug from the delayed release particles.

In the case of a basic drug the particle may be formulated with a pharmaceutically acceptable organic acid so as to maintain the micro-pH of the particle during release in the neutral pH conditions.

The matrix can consist of inert pharmaceutical substances such as well known to one skilled in the art of pharmaceutical formulation. In particular the matrix can include one or more diluants such as microcrystalline cellulose, lactose, mannitol, starch and one or more disintegrants, for example crospovidone, sodium starch glycolate and croscarmellose. Other excipients may also be included, lubricants, for example magnesium stearate, glyceryl stearate, and glyceryl behenate, binders, for example hydroxypropylmethylcellulose, ethylcellulose and povidone, glidants, for example talc and colloidal silicon dioxide.

(3) Capsule comprising one or more immediate release tablets and one or more delayed release tablets.

The delayed release tablets are prepared as described above. Immediate release tablets can be made exactly the same way, except they are uncoated, do not require a cationic surfactant and do not normally require addition of an acid. Instead of or as well as the immediate release tablet, one or more sustained (slow) release tablets may be included in the formulation.

(4) Multicoated tablets

Delayed release tablets are prepared as described above and press coated with an immediate release soluble or disintegrable coating.

List of figures:

Figure 1 shows examples *in vitro* release profiles, where the full curve shows a delayed release profile (TR), the dashed curve shows the combination of an immediate release with a delayed release profile (IR + TR), and the dotted curve shows the combination of both immediate release and sustained release profiles with a delayed release profile (IR + SR + TR).

Figure 2 shows an *in vitro* dissolution profile of the coated pellets containing alfuzosin hydrochloride of example 1.

Figure 3 shows an *in vitro* dissolution profile of the coated pellets containing alfuzosin hydrochloride of comparative example 1.

Figure 4 shows an *in vitro* dissolution profile of the coated pellets containing alfuzosin hydrochloride of example 2.

Figure 5 shows an *in vitro* dissolution profile of the coated pellets containing alfuzosin hydrochloride of example 3.

Figure 6 shows an *in vitro* dissolution profile of the coated pellets containing alfuzosin hydrochloride of comparative example 3.

The examples which follow illustrate the invention without limiting it:

Example 1: Capsules containing alfuzosine hydrochloride and cetylpyridinium chloride - slow release after a long interval

3325 g of non-pareil beads 16/18 mesh were loaded with alfuzosin hydrochloride by coating in a GPCG3 fluid bed coater-dryer with a suspension of the following condition

alfuzosin hydrochloride	5.0 %	87.5 g
Polyvinyl alcohol[1]	5.0 %	87.5 g
purified water	90.0 %	1575 g

[1] Mowiol 5-88® commercialised by Chimidis Hoechst

1100 g of these alfuzosin-coated beads were then coated in a GPCG1 fluid bed coater-dryer using a suspension of the following composition:

cetylpyridinium chloride	4.3 %	43.4 g
succinic acid	4.7 %	46.9 g
hydroxypropylmethylcellulose[2]	5.9 %	59.0 g
purified water	42.5 %	425.0 g
isopropanol	42.5 %	425.0 g

[2]Pharmacoat 603® commercialised by Shin-Etsu

Finally 1000 g of beads above described were coated using a polymer solution of the following composition:

ammonio methacrylate copolymer Type B [3]	5.1 %	119.0 g
ammonio methacrylate copolymer Type A [4]	0.3 %	7.0 g
acetylated monoglycerides[5]	0.6 %	14.0 g
isopropanol	56.4 %	1316.0 g
acetone	37.6 %	877.3 g

[3] Eudragit® RS100 commercialised by Röhm Pharma

[4] Eudragit® RL100 commercialised by Röhm Pharma

[5] Eastman 9-45 commercialised by Eastman

The dissolution of the beads was measured using the method described in the European pharmacopoeia with the rotating paddle apparatus, at a stirring speed of 100 rpm. Dissolution medium was 500 mL, 0.01M hydrochloric acid at 37°C ± 0.5°C. The amount of alfuzosine dissolved was measured by UV spectrophotometry at 330 nm. The dissolution curve obtained is shown in figure 2.

Comparative example 1: Capsules containing alfuzosine hydrochloride (without cetylpyridinium chloride)

1100 g of the alfuzosin-coated beads, prepared as described in example 1 were coated using a suspension of the following composition :

succinic acid	7.0 %	46.2 g
hydroxypropylmethylcellulose[1]	8.8 %	58.3 g
purified water	42.1 %	277.9 g
isopropanol	42.1 %	277.9 g

[1] Pharmacoat 603® commercialised by Shin-Etsu

Finally 1000 g of beads above described were coated using a polymer solution as described in example 1

The dissolution profil of the pellets was determined. The dissolution method was that described in example 1. The dissolution curve obtained is shown in figure 3.

Example 2: Coated pellets

Delayed release pellets containing alfuzosin hydrochloride, tartaric acid and cetylpyridinium chloride as cationic surfactant

1000 g of nonpareil beads 16/18 mesh were coated using a suspension with the following composition:

tartaric acid	6.0 %	78.0 g
hydroxypropylmethylcellulose [1]	4.0 %	53.0 g
cetylpyridinium chloride	3.0 %	39.0 g
triethyl citrate	1.4 %	18.2 g
purified water	43.8 %	557 g
isopropanol	43.8 %	557 g

[1] Pharmacoat 603® commercialised by Shin-Etsu

The pellets were then loaded with alfuzosin hydrochloride by coating with the following solution, in a GPCG1 fluid bed coater-dryer:

alfuzosin hydrochloride	8.3 %	78 g
povidone K30 [2]	8.3 %	78 g
ethanol	83.4 %	784 g

[2] Kollidon® commercialized by BASF

Finally 1000 g of the pellets were coated using a polymer solution of the following composition :

ammonio methacrylate copolymer Type B [3]	11.40 %	83.4 g
ammonio methacrylate copolymer Type A [4]	0.93 %	6.8 g
triethyl citrate	1.37 %	10.0 g
isopropanol	51.80 %	379.0 g
acetone	34.50 %	252.0 g

[3] Eudragit® RS100 commercialised by Röhm Pharma

[4] Eudragit® RL100 commercialised by Röhm Pharma

The dissolution profile of the pellets in 0.01 M hydrochloric acid was measured using the method described in example 1. The dissolution curve obtained is shown in figure 4.

Example 3: Coated pellets :

Delayed release pellets containing alfuzosin hydrochloride, succinic acid and cocamidopropylbetain as a zwitterionic surfactant

1000 g of nonpareil beads 16/18 mesh were coated using a suspension with the following composition,

succinic acid	5.63 %	78.0 g
hydroxypropylmethylcellulose [1]	3.82 %	53.0 g
cocamidopropylbetain [2]	2.81 %	39.0 g
purified water	43.87 %	608 g
isopropanol	43.87 %	608 g

[1] Pharmacoat 603® commercialised by Shin-Etsu

[2] Amonyl® 380LC commercialised by Seppic

The pellets were then loaded with alfuzosin hydrochloride as described in example 2

Finally 1000 g of the pellets were coated using a polymer solution of the following composition :

ammonio methacrylate copolymer Type B [3]	11.40 %	208.5 g
ammonio methacrylate copolymer Type A [4]	0.93 %	17 g
triethyl citrate	1.37 %	25 g
isopropanol	51.80 %	947.5 g
acetone	34.50 %	630 g

[3] Eudragit® RS100 commercialised by Röhm Pharma

[4] Eudragit® RL100 commercialised by Röhm Pharma

After drying in a ventilated oven, at 30°C for 24 h the dissolution profile of the pellets in 0.01 M hydrochloric acid was measured using the method described in example 1. It is shown in figure 5.

Comparative example 3: coated pellets without surfactant

1000 g of non-pareil beads 16/18 mesh were coated using a suspension with the following composition

succinic acid	5.99 %	78.0 g
hydroxypropylmethylcellulose [1]	4.07 %	53.0 g
purified water	44.97 %	585.5 g
isopropanol	44.97 %	585.5 g

[1] Pharmacoat 603® commercialised by Shin-Etsu

The beads were then loaded with alfuzosin hydrochloride according to example 1 and finally coated with polymer using the same methods and composition as described in example 3. The dissolution profiles of the pellets were measured as described in example 1. They are shown in figure 6.

Claims

1. A delayed release coated core comprising an active substance in its core and a polymer coating comprising at least one or more ammonio methacrylate copolymers, characterised in that the core comprises at least one ore more surfactants.

2. A delayed release coated core according to claim 1, characterised in that the surfactants are cationic or zwitterionic in nature.

3. A delayed release coated core according to claim 1 or 2, characterised in that the ammonio methacrylate copolymers are of type A or B.

4. A delayed release coated core according to anyone of claim 1 to 3, characterised in that the cationic surfactants are chosen among trimethyl-dimyristoyl-ammonium propionate, dimethyl-dioctadecyl-ammonium bromide, trimethyl-cetyl-ammonium bromide, dimethyl-didodecyl--ammonium bromide, benzalkonium chloride, cetylpyridinium chloride and cetrimide.

5. A delayed release coated core according to anyone of claim 1 to 3, characterised in that the zwitterionic surfactants are chosen among N-alkylbetaines, C-alkylbetaines, N-alkylamidobetaines, N-alkylglycines, phosphatidylcholines and lecithins.

6. A delayed release coated core according to claim 5, characterised in that the zwitterionic surfactant is cocamidopropylbetain.

7. A delayed release coated core according to anyone of claim 1 to 6, characterised in that the active substance is chosen among diltazem, theophylline, felodipine, verapamil, clonidine, acebutolol, alprenolol, betaxolol, metoprolol, nadolol, propranolol, timolol, captopril, enalapril, fosinopril, tiapamil, gallopamil, amlodipine, nitrendipine, nisoldipine, nicardipine, felodipine, molsidamine, indomethacin, sulindac, indoprofen, ketoprofen, flurbiprofen, fenbufen, fluprofen, diclofenac, tiaprofenic acid, naproxen, mizolastin, terbutaline, salbutamol, betamethasone, prednisone, methylprednisone, dexamethasone, prednisolone,

sumatriptan, naratriptan, cimetidine, ranitidine, famotidine, nizatidine, omeprozole, morphine, fenoprofen, ibuprofen, ketoprofen, alclofenac, mefenamic, alfuzosin, prazosin, tamsulosin, levodopa and methyldopa, their salts and pharmacologically active esters.

8. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a particle, pellet, bead, granule or spheroid, of a diameter comprised between 0.3 and 3 mm.

9. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a tablet.

10. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a minitablet.

11. A delayed release coated core according to anyone of claim 1 to 10, characterised in that the core is separated from the polymer coating by a layer of water soluble polymer.

12. A delayed release coated core according to claim 11, characterised in that said soluble polymer is chosen among hydroxypropylmethylcellulose, hydroxyethylcellulose and polyvinylpyrolidone.

13. A pharmaceutical dosage form comprising at least a delayed release coated core according to anyone of claims 1 to 12.

14. A pharmaceutical dosage form according to claim 13, characterised in that it takes the form of a tablet, a multilayer tablet, a multicoated tablet or a capsule.

15. A pharmaceutical dosage form according to claim 13 or 14, characterised in that coated cores of differing delayed release times are combined together to give "stepped" release profile.

16. A pharmaceutical dosage form according to claim 13 or 14, characterised in that the release coated core(s) is/are combined with other galenic entitie(s), which release is immediate or sustained.

17. A pharmaceutical dosage form according to claim 16, characterised in that the other galenic entitie(s) contain(s) a different active substance as in the release coated core(s).

18. A pharmaceutical dosage form according to claim 16, characterised in that a first release pulse occurs immediately and a second release pulse is delayed to a fixed time.

19. A capsule according to claim 16, characterised in that it comprises the delayed release coated cores according to claim 8 or 10 and an immediate and/or sustained release entity chosen alternatively among

(i) immediate release particles or minitablets or an immediate release granulate or powder,

(ii) controlled release particles or minitablets.

20. A tablet according to claim 16, characterised in that it comprises the delayed release coated cores according to claim 8 imbedded in a rapidly desintegrating matrix and alternatively in that

(i) the matrix is free of the active substance,

(ii) the matrix also comprises the active substance,

(iii) sustained release particles are mixed to the delayed release particles,

(iv) immediate release particles are mixed with the delayed release coated particles,

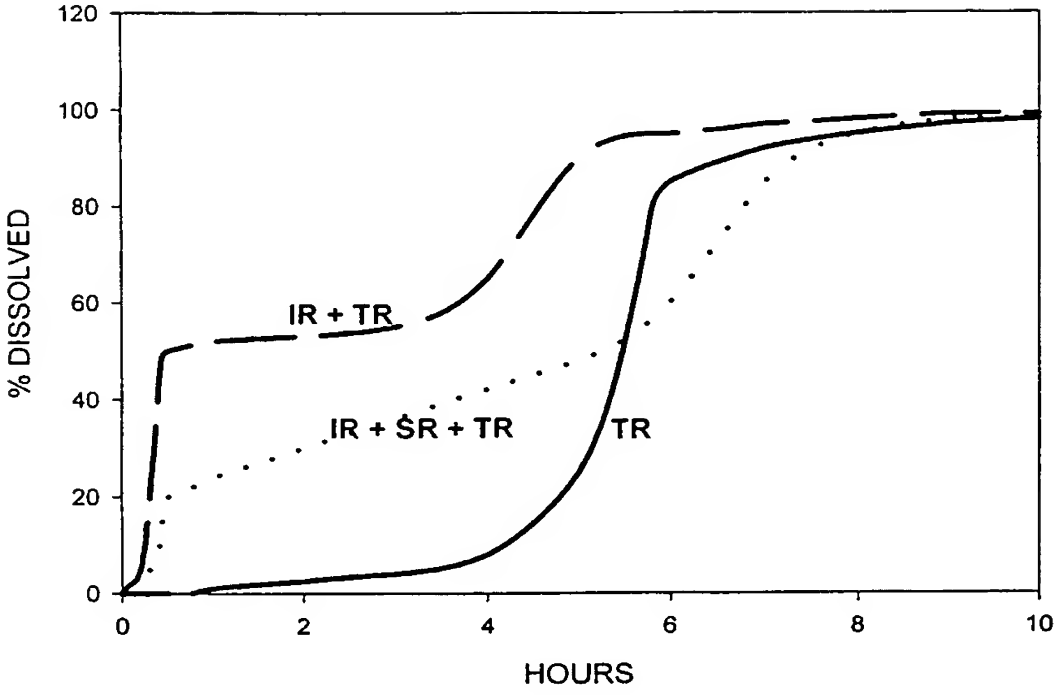
(v) the delayed release particles are further coated with a layer comprising the active substance, allowing an immediate release,

(vi) the tablet consists of one or more layers comprising the delayed release particles in the rapidly desintegreting matrix and of one or more layers comprising the active substance in an immediate release matrix.

21. Capsule according to claim 16, characterised in that it comprises one or more immediate release tablets and one or more delayed release tablets according to claim 9.

22. Multicoated tablets according to claim 16, characterised in that the tablet is coated with an immediate release soluble or disintegrable coating.

FIG. 1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IR + SR + TR
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FIG. 2

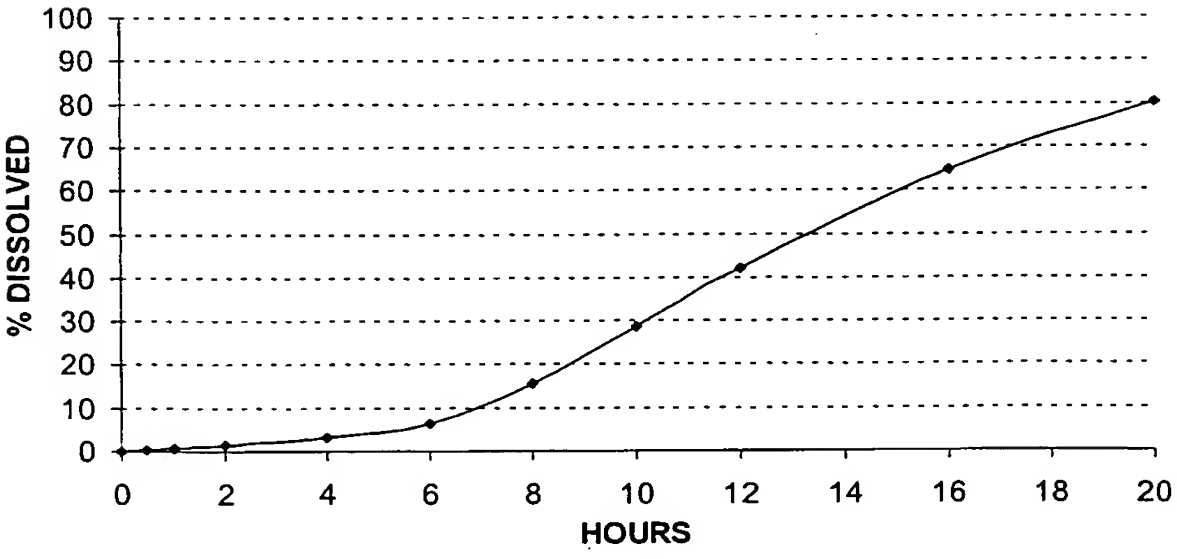
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FIG. 3

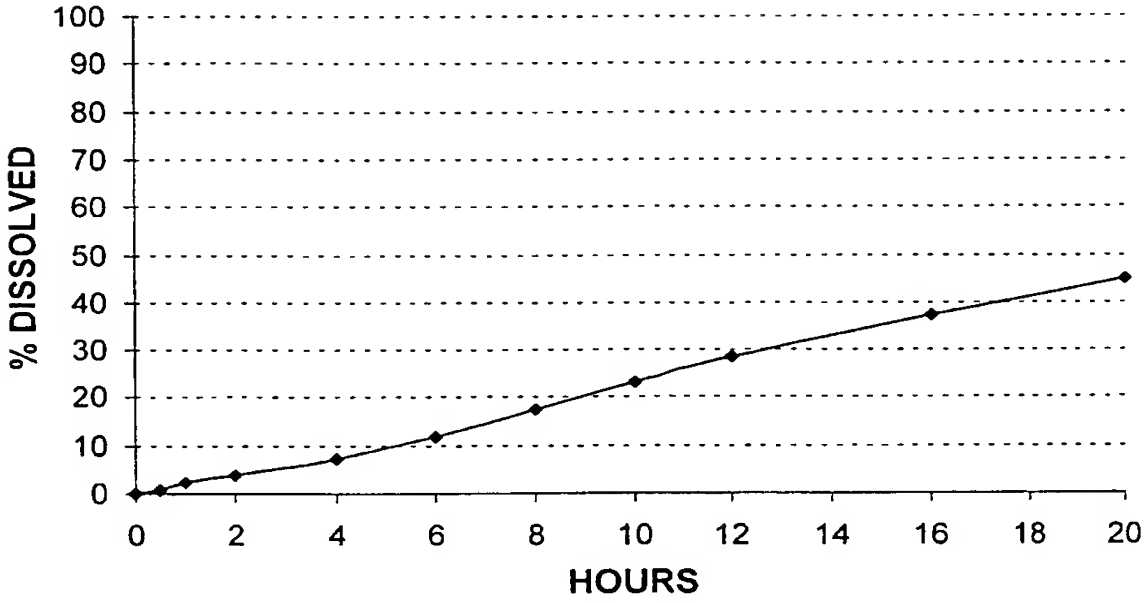
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FIG. 4

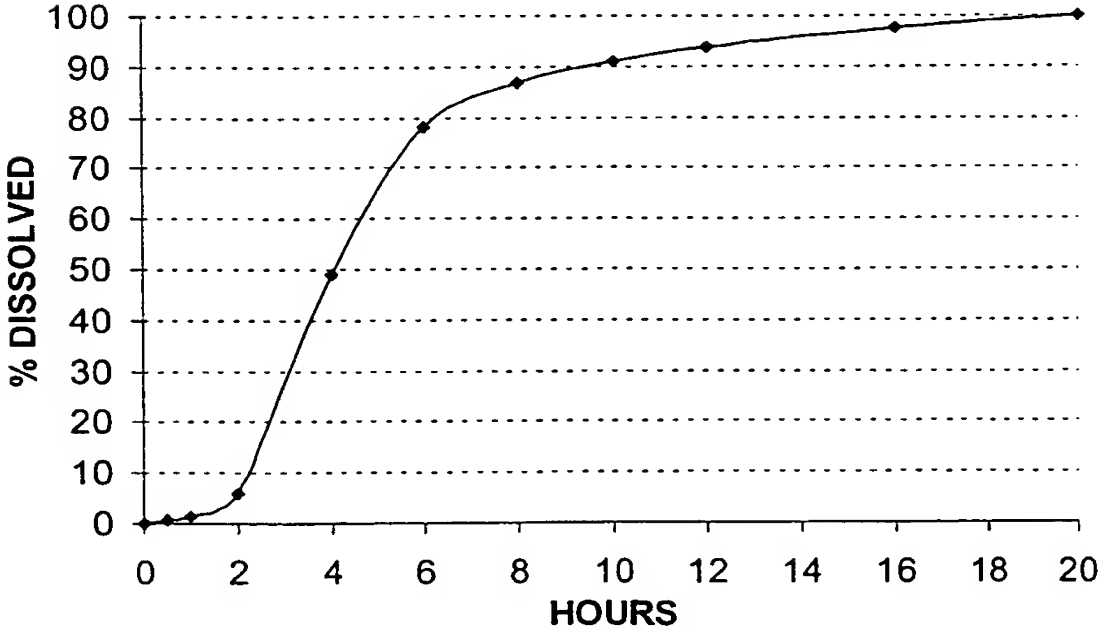
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FIG. 5

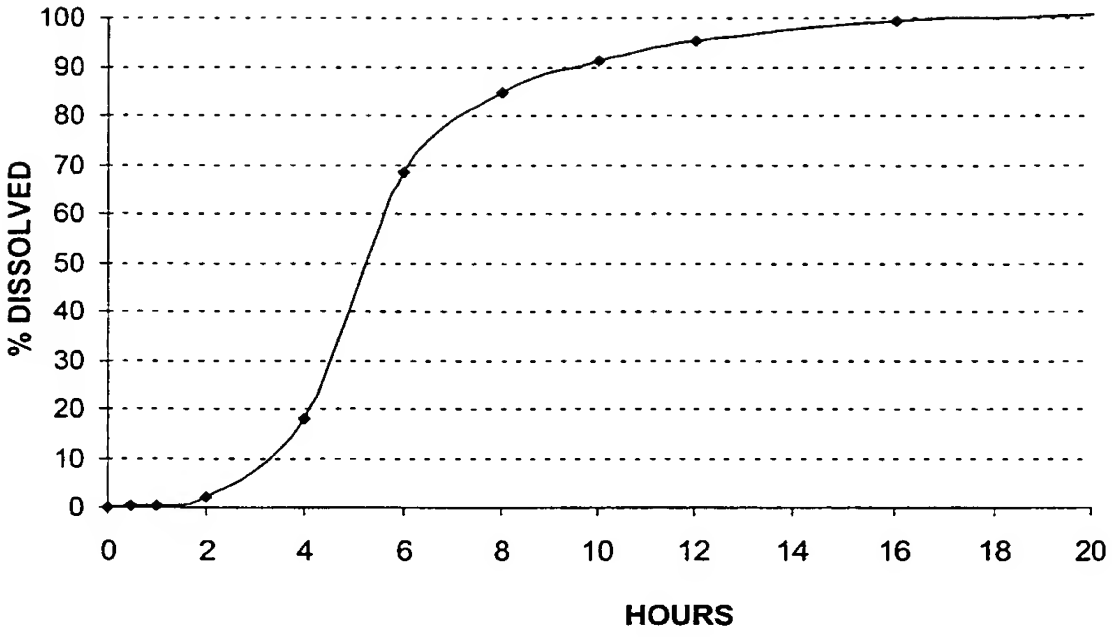
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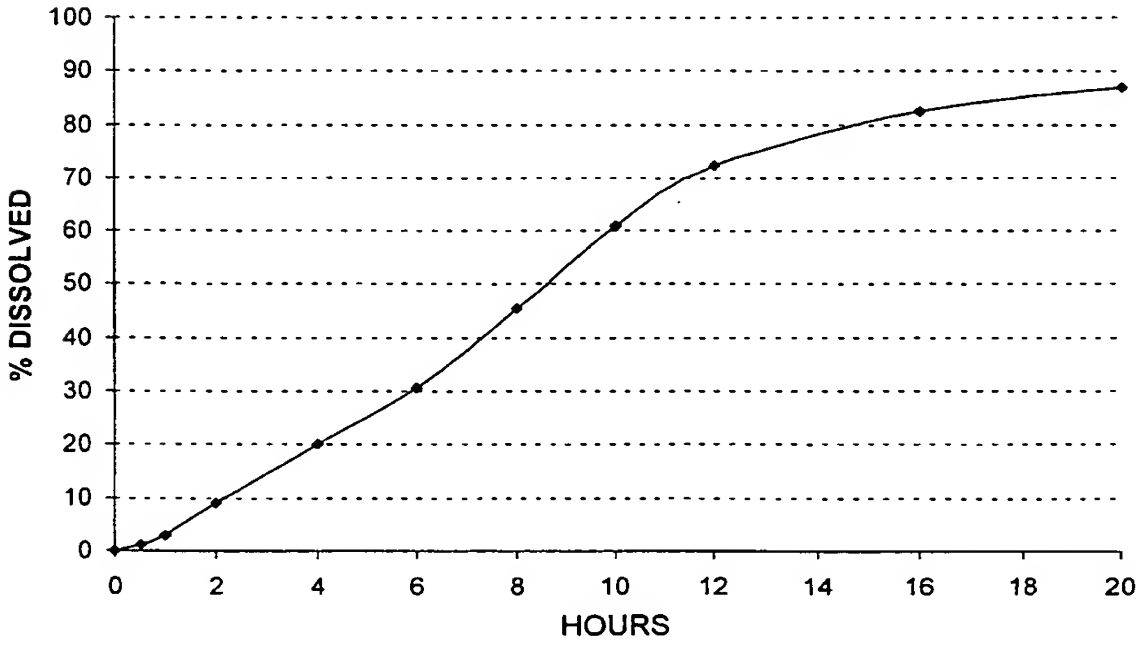
FIG. 6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HOURS

Claims

1. A delayed release coated core comprising an active substance in its core and a polymer coating comprising at least one or more ammonio methacrylate copolymers, characterised in that the core comprises at least one ore more surfactants.

2. A delayed release coated core according to claim 1, characterised in that the surfactants are cationic or zwitterionic in nature.

3. A delayed release coated core according to claim 1 or 2, characterised in that the ammonio methacrylate copolymers are of type A or B.

4. A delayed release coated core according to anyone of claim 1 to 3, characterised in that the cationic surfactants are chosen among trimethyl-dimyristoyl-ammonium propionate, dimethyl-dioctadecyl-ammonium bromide, trimethyl-cetyl-ammonium bromide, dimethyl-didodecyl--ammonium bromide, benzalkonium chloride, cetylpyridinium chloride and cetrimide.

5. A delayed release coated core according to anyone of claim 1 to 3, characterised in that the zwitterionic surfactants are chosen among N-alkylbetaines, C-alkylbetaines, N-alkylamidobetaines, N-alkylglycines, phosphatidylcholines and lecithins.

6. A delayed release coated core according to claim 5, characterised in that the zwitterionic surfactant is cocamidopropylbetain.

7. A delayed release coated core according to anyone of claim 1 to 6, characterised in that the active substance is chosen among diltazem, theophylline, felodipine, verapamil, clonidine, acebutolol, alprenolol, betaxolol, metoprolol, nadolol, propranolol, timolol, captopril, enalapril, fosinopril, tiapamil, gallopamil, amlodipine, nitrendipine, nisoldipine, nicardipine, felodipine, molsidamine, indomethacin, sulindac, indoprofen, ketoprofen, flurbiprofen, fenbufen, fluprofen, diclofenac, tiaprofenic acid, naproxen, mizolastin, terbutaline, salbutamol, betamethasone, prednisone, methylprednisone, dexamethasone, prednisolone,

sumatriptan, naratriptan, cimetidine, ranitidine, famotidine, nizatidine, omeprozole, morphine, fenoprofen, ibuprofen, ketoprofen, alclofenac, mefenamic, alfuzosin, prazosin, tamsulosin, levodopa and methyldopa, their salts and pharmacologically active esters.

8. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a particle, pellet, bead, granule or spheroid, of a diameter comprised between 0.3 and 3 mm.

9. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a tablet.

10. A delayed release coated core according to anyone of claim 1 to 7, characterised in that it is a minitablet.

11. A delayed release coated core according to anyone of claim 1 to 10, characterised in that the core is separated from the polymer coating by a layer of water soluble polymer.

12. A delayed release coated core according to claim 11, characterised in that said soluble polymer is chosen among hydroxypropylmethylcellulose, hydroxyethylcellulose and polyvinylpyrolidone.

13. A pharmaceutical dosage form comprising at least a delayed release coated core according to anyone of claims 1 to 12.

14. A pharmaceutical dosage form according to claim 13, characterised in that it takes the form of a tablet, a multilayer tablet, a multicoated tablet or a capsule.

15. A pharmaceutical dosage form according to claim 13 or 14, characterised in that coated cores of differing delayed release times are combined together to give "stepped" release profile.

16. A pharmaceutical dosage form according to claim 13 or 14, characterised in that the release coated core(s) is/are combined with other galenic entitie(s), which release is immediate or sustained.

17. A pharmaceutical dosage form according to claim 16, characterised in that the other galenic entitie(s) contain(s) a different active substance as in the release coated core(s).

18. A pharmaceutical dosage form according to claim 16, characterised in that a first release pulse occurs immediately and a second release pulse is delayed to a fixed time.

19. A capsule according to claim 16, characterised in that it comprises the delayed release coated cores according to claim 8 or 10 and an immediate and/or sustained release entity chosen alternatively among

(i) immediate release particles or minitablets or an immediate release granulate or powder,

(ii) controlled release particles or minitablets.

20. A tablet according to claim 16, characterised in that it comprises the delayed release coated cores according to claim 8 imbedded in a rapidly desintegrating matrix and alternatively in that

(i) the matrix is free of the active substance,

(ii) the matrix also comprises the active substance,

(iii) sustained release particles are mixed to the delayed release particles,

(iv) immediate release particles are mixed with the delayed release coated particles,

(v) the delayed release particles are further coated with a layer comprising the active substance, allowing an immediate release,

(vi) the tablet consists of one or more layers comprising the delayed release particles in the rapidly desintegreting matrix and of one or more layers comprising the active substance in an immediate release matrix.

21. Capsule according to claim 16, characterised in that it comprises one or more immediate release tablets and one or more delayed release tablets according to claim 9.

22. Multicoated tablets according to claim 16, characterised in that the tablet is coated with an immediate release soluble or disintegrable coating.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SANSYL002/MB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 06795	27/06/2000	28/06/1999
Applicant		
SANOFI-SYNTHELABO		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06795

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 97 23219 A (LABORATOIRES DES PRODUITS ETHIQUES ETHYPHARM) 3 July 1997 (1997-07-03) claims 1,6,14,15 page 5, line 31 - line 36 ---	1-3, 7-10,13, 14 11,12
Y	WO 95 03052 A (WARNER-LAMBERT) 2 February 1995 (1995-02-02) claim 1 page 7, line 26 -page 8, line 7 page 8, line 27 -page 9, line 22 ---	11,12
X	EP 0 386 967 A (YAMANOUCHI) 12 September 1990 (1990-09-12) claims 1-3 column 3, line 5 - line 29 column 4, line 11 - line 13 --- -/--	1,3, 7-10,13, 14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 09785 A (PROCTER & GAMBLE) 27 May 1993 (1993-05-27) the whole document	1-22
A	EP 0 908 177 A (GOLD, OSCAR) 14 April 1999 (1999-04-14) the whole document	1-22
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